Impact of Current Good Manufacturing Practices and Emission Regulations and Guidances on the Discharge of Pharmaceutical Chemicals into the Environment from Manufacturing, Use, and Disposal

Ranga Velagaleti, Philip K. Burns, Michael Gill, and James Prothro

BASF Corporation, Shreveport, Louisiana, USA

The current Good Manufacturing Practice (cGMP) and effluent emission (use and disposal) regulations of the U.S. Food and Drug Administration (FDA) and manufacturing effluent discharge and emission regulations of the U.S. Environmental Protection Agency (U.S. EPA) require contained manufacture, use, and disposal of pharmaceuticals with the goal of minimizing the release of pharmaceutical chemicals into the environment. However, debate has recently arisen in several scientific forums over whether these regulations adequately protect human and environmental health from the new pharmaceutical drugs introduced each year into the marketplace and the multitude of existing products, each with many distinct biochemical modes of actions. To address this issue, it is important to understand the relevance of current cGMP regulations and emission regulations that have a direct bearing on the releases of pharmaceutical chemicals into the environment during the manufacture, use, and disposal of active pharmaceutical ingredients (drug substances) and drug products. This knowledge may help us assess the quantity of residues that may be released into the environment. Additionally, the information on physical, chemical, and degradation and sorption properties of the pharmaceutical chemicals may help determine the net residue levels that could persist in the environment to evaluate if such residues have any bearing on human and environmental health. The scientific and regulatory aspects of issues related to the manufacture, use, and disposal of pharmaceutical chemicals are discussed in this article, with special emphasis on potential environmental exposure pathways during the life cycle of an active pharmaceutical ingredient or drug product. The mechanisms of degradation (transformation or depletion) and dilution of pharmaceutical residues that may be released into aquatic or terrestrial environmental compartments are described. Such degradation and dilution of pharmaceutical chemicals in the environment may significantly reduce the residues. It is important to evaluate whether such residue levels have any measurable impact on human and/or environmental health.
Key words: **active pharmaceutical ingredients, drugs, emissions, environment, Food and Drug Administration, Good Manufacturing Practices, regulations, U.S. Environmental Protection Agency.** ***Environ Health Perspect*** **110:213–220 (2002). [Online 5 February 2002]**
http://ehpnet1.niehs.nih.gov/docs/2002/110p213-220velagaleti/abstract.html

Pharmaceutical chemicals are used for the benefit of human and animal health. The production volumes and the use rates of most pharmaceutical active ingredients (referred to here as pharmaceutical chemicals or pharmaceuticals) in new drug products used for either human or animal health consumption are small relative to many consumer products. Pharmaceutical chemicals may be discharged into the environment at very low concentrations through their manufacture, use, and disposal. The environmental impact of such releases was the subject of several scientific reviews published recently emphasizing the perspectives from the United States and Europe (*1–5*). Daughton and Ternes (*1*), in an exhaustive review, pointed out that new pharmaceutical drugs are introduced each year to the marketplace in addition to the already existing large array of drug products. The active ingredient (pharmaceutical chemical) in each drug may have a distinct biochemical mode of action. They emphasized that the effects of the active ingredients in these drugs on the nontarget environmental species are totally unknown (*1*). The American Chemical Society (ACS)-sponsored symposium on "Pharmaceuticals and Personal Care Products—An Emerging Concern" at the ACS spring 2000 meeting, the Tulane Environmental Law Conference discussions on "Pharmaceutical Discharges in Drinking Water," and the National Ground Water Association (NGWA)-sponsored "International Conference on Pharmaceuticals and Endocrine Disrupting Chemicals in Water" (9–11 October 2001, Minneapolis, MN) focused on concerns over pharmaceuticals showing up in rivers downstream from sewage plants and in several public water systems. These conferences demonstrate a growing trend toward public debate over and concern about this issue.

As stated in the U.S. Food and Drug Administration's (FDA) *Environmental Assessment Technical Assistance Handbook* (*6*), the assessment of risk to the environment caused by the manufacture, use, and disposal of human and animal health drugs is required by FDA. Environmental Assessment reports (EAs) supported by experimental data were required by FDA for all drugs (*6*) as a part of the New Drug Applications (NDAs) for approximately 10 years (~1985–1995). In 1995, the data generated during this period regarding the behavior of more than 100 pharmaceutical drugs in the environmental matrices—such as water, soil, sediment, sludge (environmental fate, i.e., fate)—and their toxicity to environmental organisms present in these matrices (environmental toxicity) were reviewed by the FDA (*7*); on the basis of these data, the FDA reevaluated and revised its environmental regulations for human drugs and biologics (*8*). A revised guidance entitled *Guidance for Industry—Environmental Assessments for Human Drugs and Biologics Applications* (*8*) was published by the FDA. Since 1998, as per this guidance, applicants are required to provide an EA when the expected introduction concentration (EIC) of the active ingredient of the drug in the aquatic environment (EIC-aquatic) exceeds 1 ppb. Applicants were granted categoric exclusions from EA requirements if the EIC-aquatic was < 1 ppb and the drug toxicity information was favorable to such exclusion.

Against this backdrop of FDA review and revision of regulations and new requirements for EAs, recently published literature (*1–3*) and various conferences on this topic indicate that pharmaceutical chemicals might have long-term effects on environmental species, and recommendations have been made for further research to evaluate these effects. Many scientists recognize the difficulty in partitioning the effects of pharmaceuticals in the environment from effects caused by many other chemicals (consumer chemicals and other industrial chemicals including agrochemicals) present in the environment. Review of the past data indicated that the

Address correspondence to R. Velagaleti, BASF Corporation, 8800 Line Avenue, Shreveport, LA 71106, USA. Telephone: (318) 861-8040. Fax: (318) 861-8004. E-mail: velagar1@basf-corp.com

A brief narrative of this paper was presented on 9 March 2001 at the Tulane Environmental Law Conference, Panel on "Pharmaceutical Discharges in Drinking Water." R.V. thanks the organizers for extending an invitation to attend the conference. We thank V. Cooper for help with formatting the manuscript.

Received 1 June 2001; accepted 20 September 2001.

drug products with an active pharmaceutical ingredient (API) concentration at the point of entry into the aquatic environment (expected introduction concentration, EIC-aquatic) of < 1 ppb had negligible environmental effects (*7*), as seen from fate and aquatic and terrestrial toxicity (acute and chronic) data. These findings provided a rationale for < 1 ppb for categoric exclusion stated in the FDA guidance document (*8*) for human drugs and biologics. In this article we discuss regulatory and scientific aspects of pharmaceutical discharges from manufacture, use, and disposal that have a direct bearing on the release of pharmaceutical chemicals into the environment.

Manufacture of Pharmaceutical Chemicals

Manufacture of pharmaceuticals normally takes place in two stages: the synthesis/manufacture (using raw materials and synthesis intermediates) of API or bulk drug and the manufacture of the finished drug product (using the API and excipients). Emission controls and accountability for various components of APIs or drug product during manufacture, mandated by the FDA, and the comparison of actual yields with theoretical yields required by FDA current Good Manufacturing Practices (cGMPs) may preclude or minimize any significant release of drug product or excipients into the environment.

Manufacture of APIs and Drug Products

For API manufacture, appropriate raw materials are used to derive the synthesis or process intermediates, which are processed further to complete the synthesis of the bulk drug. Depending on the chemical nature of the bulk drug, the synthesis process may be a few steps or multistep process, requiring the use of few to several containers/vessels. Various steps of the manufacturing processes are designed to ensure minimal release of raw materials, intermediates, or bulk drug substance during the manufacture of APIs. Moreover, the accountability for raw materials, intermediates, and the API is a requirement defined in the GMPs for APIs by the FDA (sections VI B and VI C) (*9*). The FDA's draft API GMP document section IV B (*9*) states:

> Raw materials used for manufacturing APIs and intermediates should be weighed and measured.... Weighing and measuring devices should be of suitable accuracy for the intended use. Wherever necessary, they should be calibrated to ensure accurate results within appropriate ranges. Weighing, measuring and subdividing operations for raw materials should be adequately supervised.

Accountability of end product at each step of manufacturing is required, as stated in section VI C: "Actual yields and percentages of expected yields should be determined at the conclusion of each appropriate phase of manufacturing or processing of an API or intermediate" (*9*). Similar controls for the accountability of raw materials (API and excipients) are required under cGMPs for drug product manufacture (*10*), which state:

> Components for drug product manufacturing shall be weighed, measured or subdivided as appropriate [section 211.01(b)].... Weighing, measuring, or subdividing operations for components shall be adequately supervised[section 211.101(c)].... Actual yields and percentages of theoretical yield shall be determined at the conclusion of each appropriate phase of manufacturing, processing, packaging, or holding of the drug product. Such calculations shall be performed by one person and independently verified by a second person [section 211.103].

Effluent Discharges from API and Drug Product Manufacturing Facilities and Regulations Governing Such Discharges

The U.S. EPA regulates the emissions and effluent discharges from pharmaceutical manufacturing. Schematics of the water-flow diagram of a typical API and drug product manufacturing facility are presented in Figures 1 and 2, respectively, highlighting the emission routes for the process wastewater and air emissions. The U.S EPA has defined process wastewater as "any water that during manufacturing or processing, comes into direct contact with or results from the production or use of any raw material, intermediate product, finished product, byproduct, or waste product. According to the U.S. EPA (*11*), process wastewater includes surface runoff from the immediate process area that has the potential to become contaminated" (p. 50423).

Effluent or wastewater discharges from pharmaceutical manufacturing facilities may be direct or indirect. A facility that directly discharges treated or untreated wastewater, noncontact cooling waters or nonprocess wastewater including storm water runoff into waters of the United States is designated a direct discharger. A facility that discharges or may discharge wastewater into a publicly owned treatment works (POTW), often through a municipal sewer system, is designated an indirect discharger. Figures 1 and 2 exemplify direct and indirect discharge scenarios, respectively. Most facilities, whether direct or indirect dischargers, have in-plant control technologies that include controls or measures applied within the manufacturing process to reduce or eliminate pollutant and hydraulic loading. Technologies applied directly to wastewater generated by the manufacturing processes include steam stripping and cyanide destruction. Process wastewater can be directed to a process wastewater collection system, which is a piece of equipment, structure, or transport mechanism used in conveying or storing a process wastewater stream. Examples of equipment used for process wastewater collection include individual drain systems, wastewater tanks, surface impoundment, and containers. In addition, end-of-pipe (EOP) treatment facilities or systems are used to treat process wastewater and nonprocess wastewater, including storm water runoff, after the wastewater stream has left the process area of the facility and before discharge.

All pharmaceutical manufacturing facilities are subjected to various degrees of restrictions or schedules of compliance with regard to processed or nonprocessed effluent discharges. These are established by the state and federal EPA and include restrictions on quantities, rates, and concentrations of chemical, physical, biologic, and other constituents that are discharged from point source into waters of the United States, the waters of the contiguous zone, or the ocean. Maximum daily discharge limitation, the highest allowable daily discharge of pollutants measured during a calendar day or any 24-hr period that reasonably represents a calendar day for the purposes of

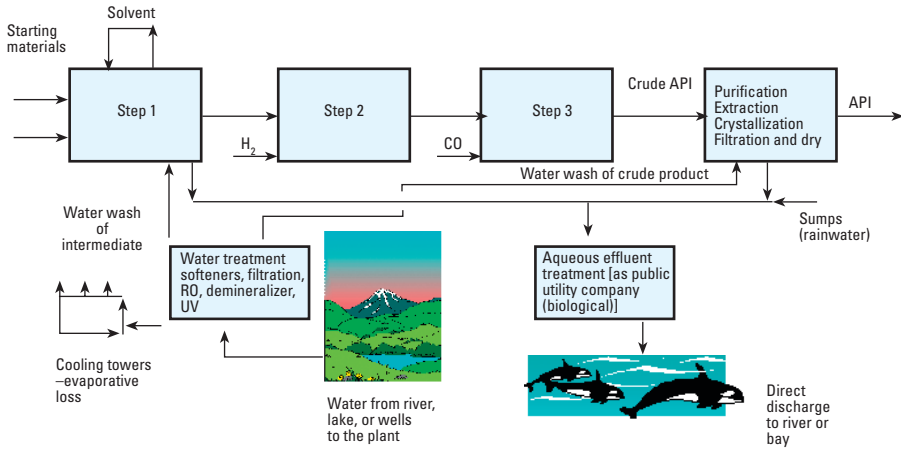

Figure 1. Schematic diagram of water flow at a typical API manufacturing facility.

sampling, are established for various listed pollutants. Also established are average monthly discharge limitations, which are the highest allowable average daily discharges over a calendar month calculated as the sum of all daily discharges measured during a calendar month divided by the number of daily discharges measured during that month. Five-day biochemical oxygen demand (BOD_5), chemical oxygen demand (COD), total oxygen-consuming capacity, total suspended solids (TSS), pH, and cyanide determinations for effluents are required at predetermined intervals.

Residues in process wastewater undergo biologic and chemical (hydrolysis and photolysis) degradation by vigorous aeration and/or exposure to sunlight. Degradation (biotransformation and hydrolytic and photolytic degradation) and depletion (mineralization due to CO_2 production) could lead to reduction of chemical residues in the collection systems. For example, during solid oral-dosage drug product manufacture, drug residues will be released predominantly through the cleaning operations including equipment used for coating, blending, tablet compression, and packaging operations. Excipients and active ingredients may become part of the process waste stream as a result and may degrade during the treatment of process wastewater and/or in the domestic sewage.

Pharmaceutical Manufacturing Effluent Limitation Guidelines

The Federal Water Pollution Control Act (Clean Water Act) amendments of 1972 established a comprehensive program to "restore and maintain the chemical, physical and biological integrity of the Nation's waters" [quoted in 40 CFR Parts 136 and 439 (*11*)], under which the U.S EPA issued effluent limitation guidelines, pretreatment standards, and new source performance standards for industrial discharges. The regulations (*11*) for effluent limitation guidelines and standards of performance and analytic methods for the pharmaceutical manufacturing point source category are applicable to all pharmaceutical manufacturing facilities. For rule making, the U.S EPA has defined four types of pharmaceutical manufacturing operations or processes and subcategorized them into:

- Subcategory A: Fermentation
- Subcategory B: Natural extraction
- Subcategory C: Chemical synthesis
- Subcategory D: Formulating, mixing, and compounding
- Subcategory E: Research that was excluded from the current regulation beyond the existing Best Practicable Control Technology (BPT) regulation promulgated on 27 October 1983 (*11*).

Various standards were considered in the current ruling for each of these categories (*11*):

- The BPT currently available
  1. BPT limitations apply to all discharges from existing direct dischargers.
  2. COD based on advanced biologic treatment for subcategories A–D.

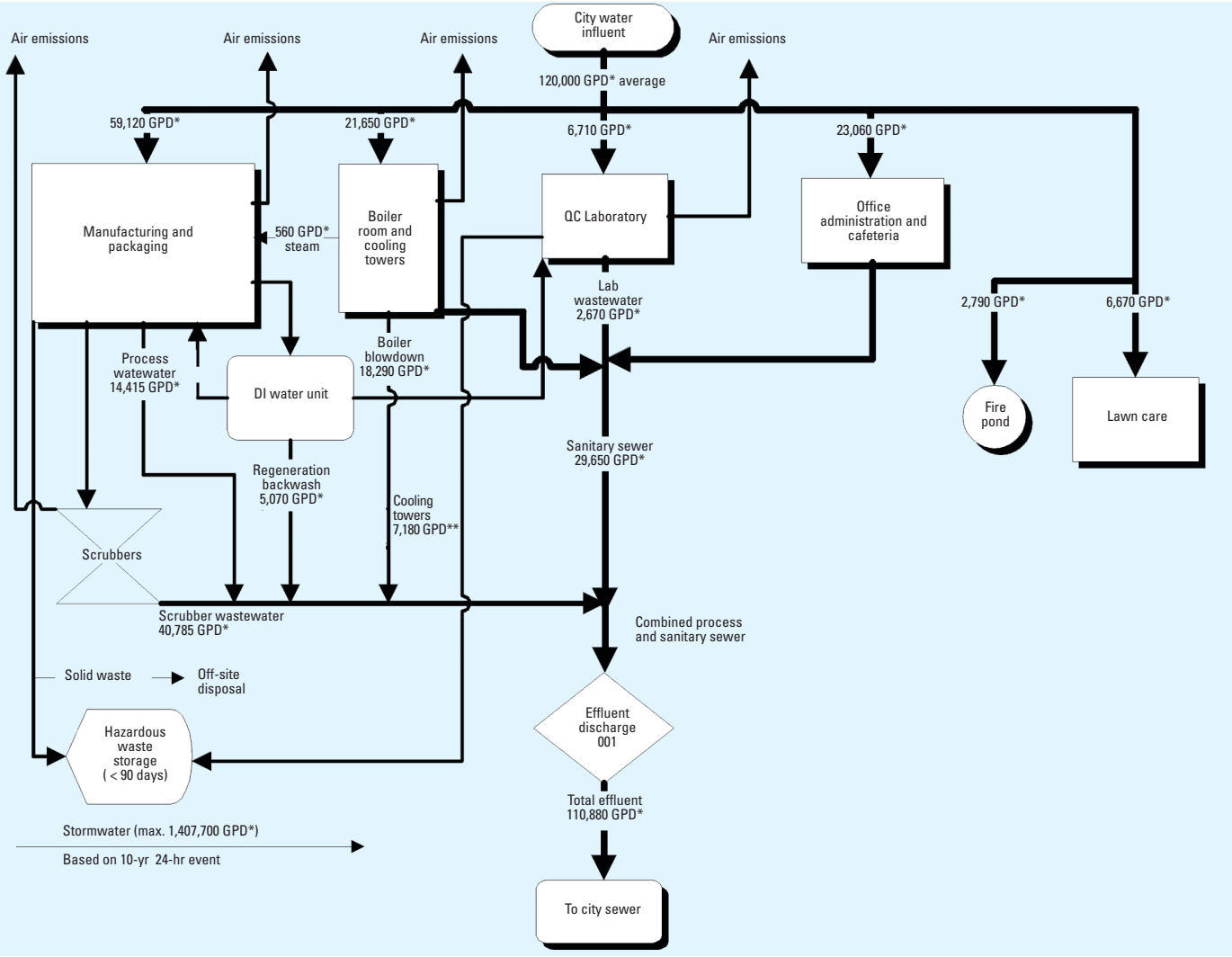

Figure 2. Schematic diagram of water flow at a typical drug product manufacturing facility.
DI, deionized; GPD, gallons per day; GPD*, based on design flow calculation from engineering design drawings of the facility; GPD**, loss due to evaporation; QC, quality control.

3. BPT limitations for BOD, TSS, and cyanide will continue to apply except for subcategories B and D, where BPT limitations for cyanide are withdrawn.

- The best available technology economically achievable (BAT)
  1. BAT limitations for subcategories B and D operations include only the pollutant COD based on advanced biological treatment. Cyanide limitations do not apply to B and D.
  2. New end-of-pipe BAT limitations for 30 organic pollutants, ammonia, and COD for subcategory A and C facilities based on advanced biological treatment only.
  3. BAT limitations apply to the Best Conventional Pollutant Control Technology (BCT) users.
- New source performance standards (NSPS)
  1. NSPS are based on the best available demonstrated control technology.
  2. New plants have the opportunity to install the best and most efficient production processes and wastewater treatment technologies, and as a result NSPS should represent the most stringent numeric values attainable through BAT technology for conventional, nonconventional, and toxic pollutants.
- Pretreatment standards for existing sources (PSES)
  1. PSES are designed to prevent the discharge of pollutants that pass through, interfere with, or otherwise are incompatible with the operation of POTWs.
  2. The regulations authorize the EPA to establish permanent standards for pollutants that pass through POTWs or interfere with POTW treatment processes or sludge disposal methods.
  3. Pretreatment standards should be analogous to the BAT effluent limitation guidelines for removal of toxic pollutants.
- Pretreatment standards for new sources (PSNS)
  1. PSNS are designed to prevent the discharge of pollutants that pass through, interfere with, or otherwise are incompatible with the operation of POTWs and issued at the same time as NSPS.
  2. The BAT technology should be incorporated to achieve PSNS.

Environmental Exposure Pathways and Degradation Mechanisms

The environmental exposure pathways for pharmaceutical manufacturing effluents are shown in Figure 3. Table 1 shows scenarios of degradation of pharmaceutical residues in the environment leading to reduction through formation of smaller molecular entities through biotransformation, hydrolysis, and photolysis, and elimination as a result of mineralization.

The concentration of the components present in the effluents can be reduced to levels permitted by regulations for direct discharge into surface waters or indirect discharge to POTW via municipal sewers through the use of appropriately designed collection systems for on-site process wastewater treatment. These treatments may facilitate biologic (biotransformation/mineralization) and/or chemical degradation (hydrolysis/photolysis). Process wastewater in direct discharge facilities is treated extensively because direct discharges expose the aquatic environment to any chemical residues remaining.

The POTWs are designed to facilitate degradation of organic molecules present in the sewage coming from municipal sewers. Extensive biodegradation (biotransformation and mineralization) is possible in the activated sludge aeration tanks where the microbial load is high due to continuous aerobic multiplication of microbes. Biotransformation of an organic molecule can occur through one or

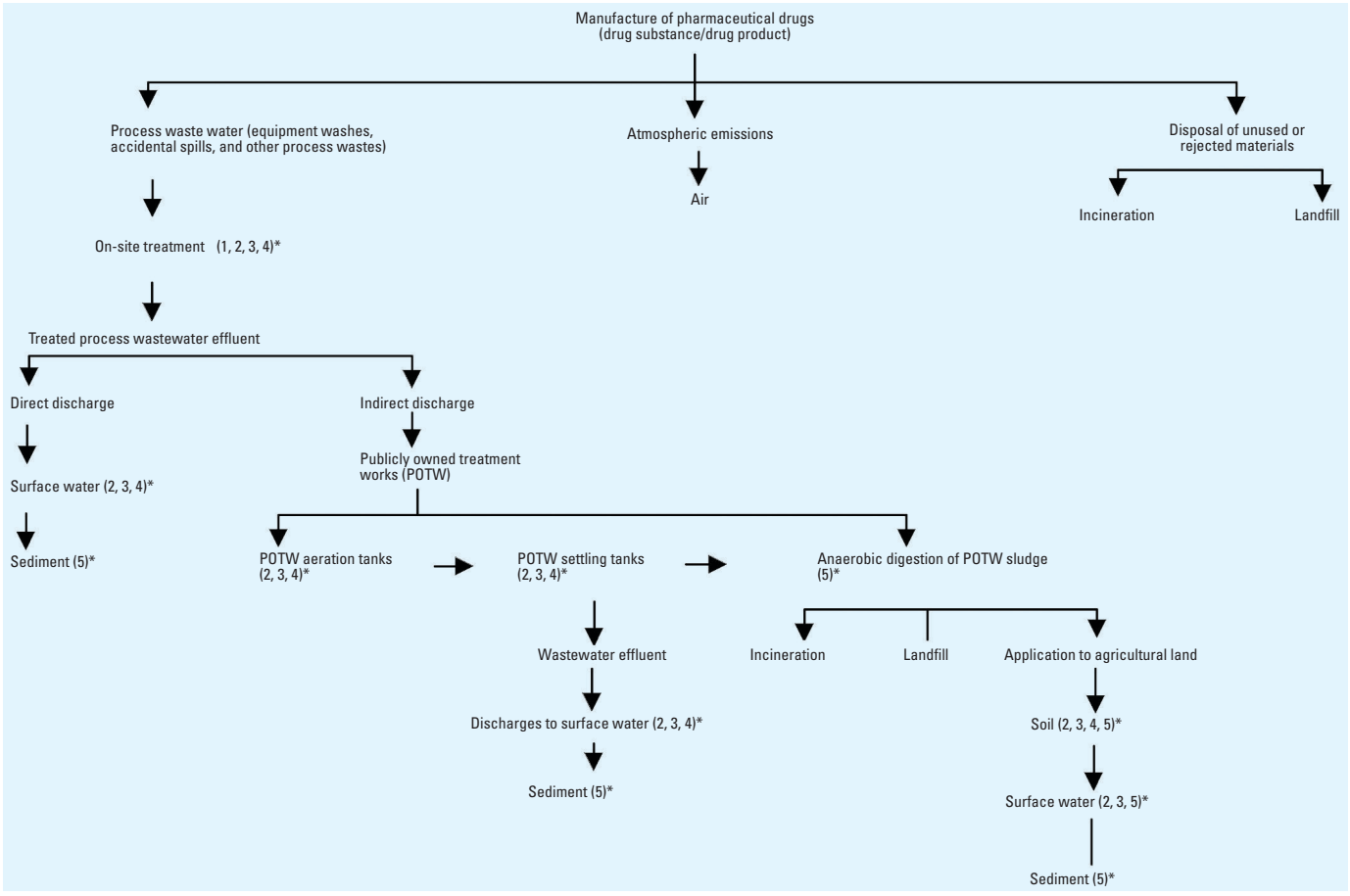

Figure 3. Environmental exposure pathways for effluents from pharmaceutical manufacturing.
*Refers to Table 1, in which pathways of degradation of pharmaceutical chemicals are discussed under items 1–5.

more of the following mechanisms: oxidation, oxidative dealkylation, decarboxylation, epoxidation, aromatic hydroxylation, aromatic nonheterocyclic ring cleavage, aromatic heterocyclic ring cleavage, hydrolysis, dehalogenation, and nitroreduction (*12*).

Chemical degradation processes such as hydrolysis and photolysis could reduce the concentration of pharmaceutical residues in the effluents. Hydrolysis is a key reaction of organic compounds with water. The chemical reaction is mediated by a direct displacement of a chemical group by the hydroxyl group (*12*). Hydrolysis could lead to partial or complete chemical transformation, depending on the susceptibility of a given organic molecule (Table 1).

The components in the waste effluents can also be degraded if they are exposed to natural sunlight, either by direct photodegradation or indirect photodegradation. Direct photodegradation by natural sunlight occurs in pharmaceutical compounds or their intermediates that have absorbance in the range of 290–800 nm. Pharmaceutical compounds that do not absorb in the 290–800 nm range can also be photodegraded through indirect photodegradation when one or more of the chemical components (sensitizers) present in the waste effluent absorb light in this region and transfer the excitation energy to and facilitate the degradation of nonabsorbing pharmaceutical residues (Table 1). Photodegradation can occur through any of the following mechanisms: fragmentation into free radicals or neutral molecules, rearrangement and isomerization reactions, photoreduction, dimerization and other addition reactions, photoionization, and electron transfer (*12*).

The wastewater and the sludge solids are separated during processing at the POTW. Organic molecules that have a high octanol/water partition coefficient (K_{ow}) and high adsorption coefficient (K_{oc}) tend to partition into sludge solids. The sludge solids at many POTWs are subjected to anaerobic digestion where anaerobic biodegradation of most organic molecules typically produces methane, CO_2, and biotransformed products. These degradation processes may substantially reduce drug residues that have entered the POTW, before the effluents are released from the POTW into aquatic or terrestrial environmental compartments (Table 1).

Discharge of processed wastewater from pharmaceutical manufacturing plants to surface waters or wastewater effluent from the POTW to surface waters will facilitate further dilution of residues. Similarly, residues in POTW sludge solids are diluted when applied to soil. Aerobic biodegradation, hydrolysis, and photodegradation could be the main pathways of degradation in surface waters. Aerobic biodegradation is the major pathway of degradation in soils. Anaerobic biodegradation is the major pathway of degradation in sediments of surface waters. Minor pathways of degradation are hydrolysis and photolysis in moist surface soils and hydrolysis and anaerobic biodegradation in deeper layers of soil (Table 1).

It is difficult for pharmaceuticals that have poor water solubility and have high octanol/water partition coefficient and that therefore bind strongly to soil to reach deep groundwater aquifers present in the United States. Therefore, pharmaceutical residues are unlikely to be detected in groundwater except when the groundwater table is too close to the soil surface (for example, in coastal states), and/or the residues are highly soluble and have low soil adsorption coefficients. When residues are present in groundwater, they may be degraded through hydrolysis and aerobic and anaerobic biodegradation.

Table 1. Pathway of degradation of pharmaceutical chemicals at the on-site process wastewater treatment facility, domestic sewage, POTW and surface waters, sediment and soil.

Pathway	Description
1. Metabolism in human/animal body	Partial or complete biotransformation (degradation): drug ⇒ drug + metabolites Partial mineralization with biotransformation products and CO_2 (partial mineralization and depletion): drug ⇒ drug + degradates + CO_2 production (depletion due to expired CO_2)
2. Aerobic biodegradation (on-site treatment, domestic sewage, POTW, surface waters, soil)	Partial or complete biotransformation (degradation): drug ⇒ drug + metabolites Partial mineralization with biotransformation products and CO_2 production (partial mineralization and depletion): drug ⇒ drug + metabolites + CO_2 production Complete mineralization (depletion): drug ⇒ CO_2 production
3. Hydrolysis (on-site treatment, domestic sewage, POTW, surface water, soil)	Partial or complete chemical transformation (degradation): drug ⇒ drug + degradates or drug ⇒ degradates
4. Aqueous photolysis (on-site treatment, POTW, surface water, moist surface of soil)	Partial or complete light mediated chemical transformation (degradation) under direct simulated artificial sunlight or direct sunlight – direct photodegradation: drug ⇒ drug + degradates or drug ⇒ degradates Partial or complete light mediated chemical transformation (degradation) under direct simulated artificial sunlight or direct sunlight with a chemical sensitizer–indirect photodegradation: drug ⇒ drug + degradates or drug ⇒ degradates
5. Anaerobic degradation (domestic sewage, POTW sludge, sediment, deeper soil layers)	Partial or complete biotransformation (degradation): drug ⇒ drug + degradates Partial mineralization with biotransformation products and CO_2 and CH_4 production (partial mineralization and depletion): drug ⇒ drug + degradates + CO_2 production + CH_4 production

Use of Pharmaceutical Chemicals

Human health. Use of drugs to maintain or improve human health is widespread. For example, drugs such as antihypertensives are consumed by millions of patients daily. These and other drugs used by consumers are likely to be metabolized in the human body and the drug residues excreted through urine and feces. The excreted drug residues may include the drug substance and/or its structurally related substances such as the dissociated parent compound, metabolites, conjugates, or degradates (drug residues), which will become part of domestic sewage. Topical applications such as antibiotics and steroids may be washed off the skin as well as metabolized in the body. Both washoff and metabolites in the excreta form a part of domestic sewage. Domestic sewage is carried through the municipal sewer system to the POTW, and during this transit drug residues may undergo biodegradation and hydrolysis. The fate of drug residues during the processing of domestic sewage at the POTW has been explained above, as well as the fate of residues in the POTW wastewater effluents in surface water and sediment and the fate of residues in the POTW sludge in soil. The environmental exposure pathways for drug residues from human and animal health uses are presented in Figure 4. In this section we focus on guidance and regulations on releases to the environment caused by the use of pharmaceutical chemicals.

Under the mandate of NEPA, FDA requires categoric exclusions or full EAs by

drug applicants (*8*). FDA guidance (*8*) on this subject provides a description of when categoric exclusions are granted and when full EAs are required. Classes of actions stated below are subject to categoric exclusions because, as a class, these actions individually or cumulatively do not significantly affect the environment. An applicant filing for approval of a drug is not required to submit an EA if a categoric exclusion is claimed under any one of these five items:

1. New drug applications (NDAs), abbreviated new drug applications (ANDAs), applications for marketing approval of a biologic product, and supplements to such applications if FDA's approval of the application does not increase the use of the active moiety;
2. NDAs, ANDAs, and supplements to such applications if FDA's approval of the application increases the use of active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be < 1 ppb;
3. NDAs, ANDAs, applications for marketing approval of a biologic product, and supplements to such applications for substances that occur naturally in the environment when the approval of the application does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment;
4. Investigational new drugs (INDs); and
5. Applications for marketing approval of a biologic product for transfusable human blood or blood components and plasma.

The specific item (1–5) under which categoric exclusion is claimed should be stated in the application with a statement that to the applicant's knowledge no extraordinary circumstances exist. The extraordinary circumstances are defined in the FDA guidance (*8*).

As stated above, if the estimated concentrations at the point of entry into aquatic environment exceed 1 ppb, then environmental assessments may be required with the applications. The method of estimating expected introduction concentrations and the qualifiers to this estimate as stated in the FDA guidance (*8*) are described below.

Expected Introduction Concentration

The FDA (*8*) in the guidance document defines EIC as "the concentration, based on fifth year-marketing estimates, of the active moiety (drug substance/API) that can enter the environment due to human use. Depletion mechanisms that occur prior to introduction into the environment and human metabolism may be considered in the calculation" (p. 38). Based on marketing estimates, if the amount produced is not the highest in the fifth year, the year of maximum production is taken into consideration for the EIC. The EIC at the point of entry into the aquatic environment in parts per billion is calculated by the following equation provided in FDA guidance (*8*):

$$A \times B \times C \times D,$$

where A = kilograms per year produced for direct use as active moiety (maximum production/year in a 5-year production cycle based on marketing estimates); B = 1/liters per day entering the POTW, estimated as 1.214×10^{11} (*8*); C = year/365 days; and $D = 10^9$ µg/kg (conversion factor).

Based on this equation, EIC-aquatic of 1 ppb = 44,300 kg of active ingredient of drug per year. Categoric exclusions are not granted if the EIC is > 1 ppb, with few exceptions (described below).

The Assessment of Environmental Risk Based on EIC

In general, pharmaceutical active ingredients are produced in smaller quantities (unless they are large-volume drugs), producing an estimated EIC of < 1 ppb, and are generally granted categoric exclusion by FDA. Under the definition of EIC, human metabolism and depletion mechanisms that occur before introduction into the environment (such as in the POTW) may be considered in the calculation. Taking the example described above, where the EIC-aquatic of 1 ppb = 44,300 kg/year, the known potential for degradation and depletion may reduce the EIC. If it is assumed that the drug is metabolized to CO_2 in the human body to the extent of 10% (0.1 ppb), the revised EIC will be 0.9 ppb. In such case, a categoric exclusion is granted. If biodegradation and chemical degradation in the POTW account for another 20% (0.18 ppb), the EIC can be further revised to 0.72 ppb. Adjustments to the EIC can be made to provide an expected environmental concentration (EEC), where EEC = EIC – depletion, dilution, and/or partitioning (Table 2). According to the FDA, a dilution factor of 10 can be applied when the wastewater effluents are released from the POTW to surface waters. The EEC in surface water using the above example will be 0.072 ppb.

Similarly, EEC estimations can be made for POTW sludge solids. The FDA estimates (*8*) suggest that approximately 54% POTW sludge solids are applied to land, and the remainder is either incinerated or landfilled. Brady (*13*) estimated that the application of organic amendments to soils would dilute agricultural soils 1,000-fold. The EEC estimations for sludge solids can take into account the amount applied to land and the 1,000-fold dilution to arrive at EEC in soil. A scenario for degradation and depletion of human drugs is presented in Table 2. We assumed that the drug will partition 90% to POTW wastewater effluent and 10% to

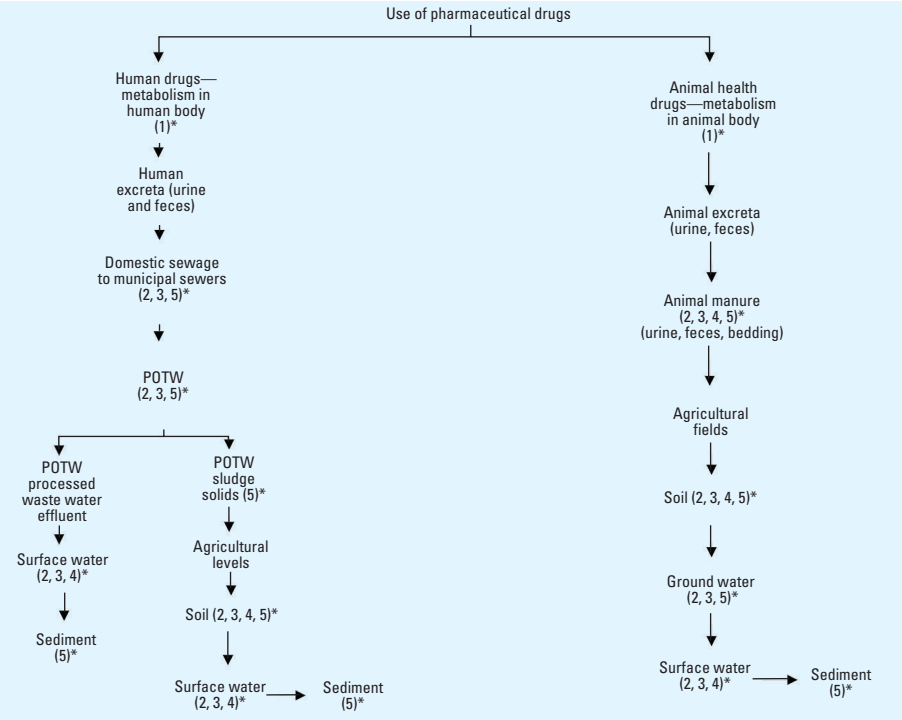

Figure 4. Environmental exposure pathways for drug residues resulting from human and animal health use.
*Refers to Table 1, in which pathways of degradation of pharmaceutical chemicals are discussed under items 1–5.

POTW sludge. More realistic estimates can be made based on known partitioning behavior (octanol/water partition coefficient and/or sludge adsorption coefficient) and solubility of chemicals. Such estimates will be required for drugs with EIC-aquatic of > 1 ppb.

Environmental Effects of Released Substances

The FDA guidance (*8*) considers the following half-life ($t_{1/2}$) estimates (equal to or less than) as rapid depletion mechanisms that will warrant no further fate or effects tests: hydrolysis, 24 hr; aerobic biodegradation in water, 8 hr; soil biodegradation, 5 days. If rapid and complete depletion mechanisms are identified, a microbial inhibition test to assess the ability of the drug or biologic substance(s) of interest to inhibit microorganisms and subsequently disrupt waste treatment processes at the POTW (by inhibiting microbial population) is recommended. Under this scenario, no further effects testing is needed. If rapid depletion mechanisms are not identified, and if log K_{ow} is ≤ 3.5, a tier 1 acute toxicity test with one species is recommended. If the EC_{50} or LC_{50} from the tier 1 acute test divided by maximum expected environmental concentration (MEEC = EIC or EEC, whichever is greater) is ≥ 1,000 (EC_{50} or LC_{50} divided by MEEC), no further testing is required.

The FDA recommends that the effects tests, when required, be designed appropriately so that a no-observed-effect concentration (NOEC) can be determined. In the tiered approach to effects testing (*8*), the toxicity test results (LC_{50}, EC_{50}, or NOEC) should be compared with estimated environmental concentrations (EIC, EEC, or MEEC) and assessment factors with conclusions on risk or no risk to the environment. In the tier 1 acute toxicity test, if there are observed effects at concentrations less than or equal to MEEC, tier 3 testing may be warranted. If the EC_{50} or LC_{50} divided by MEEC is less than the assessment factor of 1,000, tier 2 testing should be performed, which normally includes an acute toxicity base set (aquatic and/or terrestrial, depending on the partitioning behavior of the drug or biologic substance into water and sludge matrices). The aquatic toxicity base set normally includes *a*) fish acute toxicity test; *b*) aquatic invertebrate toxicity test (such as *Daphnia* acute test); and *c*) algal species bioassay test. The terrestrial toxicity base set includes *a*) plant early growth test; *b*) earthworm toxicity test; and *c*) soil microbial toxicity test. If the EC_{50} or LC_{50} for the most sensitive test organism in the base set divided by the MEEC is equal to or greater than a tier 2 assessment factor of 100, then no further testing is necessary, unless sublethal effects are observed at test concentrations at or below MEEC, in which case tier 3 chronic toxicity testing is required. Tier 3 testing will also be required if the EC_{50} or LC_{50} for the most sensitive test organism in the base set divided by MEEC is less than the tier 2 assessment factor of 100. If the chronic LC_{50} or EC_{50} divided by MEEC is equal to or greater than the assessment factor of 10, no further testing is necessary, unless sublethal effects are observed at test concentrations at or below the MEEC. The sponsor of the application is asked to consult with the FDA [Center for Drug Evaluation and Research (drugs) or Center for Biologics Evaluation and Research (biologics)] if the chronic EC_{50} or LC_{50} divided by MEEC < 10 or sublethal effects are observed at test concentrations at or below MEEC. The toxicity testing should demonstrate that pharmaceutical residues present no environmental risk. The FDA may reject the application if adverse environmental effects are noted at the MEEC levels.

Therefore, as described above, there is a systematic approach defined by the FDA to evaluate the effects of pharmaceuticals released into the environment through human use (*7*).

Use of Animal Health Drugs

Pharmaceutical chemicals are used to control diseases in food and nonfood animals. The food animals (including commercial aquaculture) are intensively reared, and when most or all of a confined group of animals are treated with a pharmaceutical chemical, the releases of residues from these animals cause environmental exposure (terrestrial and aquatic), especially through application of waste/manure to agricultural fields. If the waste/manure is landfilled or incinerated, environmental exposure is not an issue. Nonfood animals (e.g., domestic pets) are not intensively reared, and the individual uses of pharmaceutical chemicals for the health of these animals poses no risk to the environment, as the domestic waste often ends in municipal landfills. The environmental exposure pathways and degradation and depletion mechanisms for pharmaceutical chemical residues from animal health use are similar to human use (Tables 1 and 2; Figures 3–5), except that the POTW route is not involved.

Similar to the retrospective review conducted by the FDA, the Animal Health Institute in the United States conducted a retrospective review of ecotoxicity data submitted to the FDA's Center for Veterinary Medicine (CVM) from 1973 to 1997 (*14*). Also in 1997 an additional effort was made to provide a uniform procedure to estimate predicted environmental concentration (PEC) for the residues of veterinary medicines in soil (*15*). Based on the retrospective review and rationalization of PEC estimates, the International Conference on Harmonization for Veterinary Medicinal Products (VICH) comprising the European Union, the United States, and Japan, issued "Environmental Impact Assessments (EIAs) for Veterinary Medicinal Products (VMPs)—Phase I" in June 2000 (*16*). In this guidance a PEC trigger of 100 µg/kg (100 ppb) (PEC_{soil}) was provided for veterinary drugs. Following VICH guidance, if the PEC of a pharmaceutical chemical in

Table 2. A scenario of degradation and dilution of human drugs.

1. Annual production of a drug = 44,300 kg/year = 1 ppb EIC-aquatic
2. Metabolism in the human body and adsorption/depletion of 20% drug residue, 1 ppb – 20% (0.2) = 0.8 ppb
3. Hydrolysis/photolysis ($t_{1/2}$ = 5 days), biodegradation ($t_{1/2}$ = 8 hr), and depletion of 50% drug residue during its residence time in POTW, 0.8 ppb – 50% (0.4 ppb) = 0.4 ppb
4. Partitioning of the drug into POTW sludge (10%) and wastewater effluent (90%) at POTW 0.4 ppb, 0.04 ppb in POTW sludge and 0.36 ppb in the wastewater effluent
5. Dilution factor of 10 applied to POTW wastewater effluent discharges to surface water, 0.36 ppb ÷ 10 = 0.036 ppb in surface water
6. Of the drug partitioned to POTW sludge, 20% is depleted during anaerobic digestion at POTW, 0.04 × 20% (0.008) = 0.032; 57% of POTW sludge is applied to land, 0.032 ppb × 57% = 0.02 ppb POTW is applied to land, dilution factor of 1,000 is applied to POTW sludge amendment to agricultural land 0.02 ppb ÷ 1,000 – 0.00002 ppb in soil.

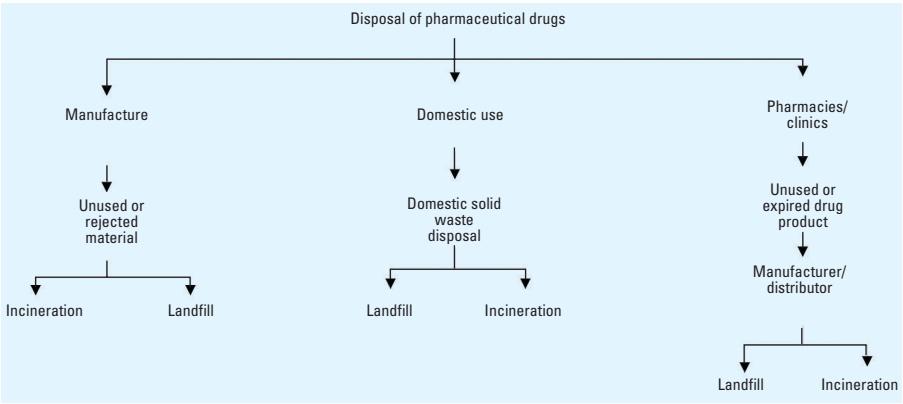

Figure 5. Environmental exposure pathways of disposed pharmaceutical drugs.

soil is 100 ppb (PEC_{soil}) for nonaquatic food animals, a phase II study is triggered by this guidance. The PEC_{soil} can be adjusted to take into account the residue depletion and metabolism in target animals. However, from aquaculture facilities, if the $EIC_{aquatic}$ is > 1 µg/L, a phase II investigation is triggered (*16*). The Committee for Veterinary Medicinal Products (CVMP) of the European Agency for the Evaluation of Medicinal Products (EMEA) issued phase II guidance in 1998 (*17*). This guidance illustrates the studies to be conducted to demonstrate a risk or no-risk scenario for the use of pharmaceutical chemicals that exceed phase I trigger values. Environmental Risk Assessments (ERAs) based on the phase II data are required before pharmaceutical chemicals are approved for use by the regulatory authorities. A similar approach is followed for ERAs in the United States and Japan, although individual country requirements may differ slightly.

Disposal of Pharmaceutical Chemicals

The disposal of unused expired or returned APIs or drug products is scrutinized under material accountability of cGMP regulations. As stated in cGMPs for APIs (*9*), "Records of returned APIs and intermediates should be maintained and should include the name, batch or lot number, reason for the return, quantity returned, date of disposition, and ultimate disposition" (section J). cGMPs for finished drug products state (*10*): "Records of returned drug products shall be maintained and shall include the name and label potency of the drug product dosage form, lot number (or control or batch number), reason for the return, quantity returned, date of disposition, and ultimate disposition of the drug product" (Section 211.204). Under the ultimate disposition status to destroy, most of the pharmaceutical compounds are disposed of through incineration or landfilling in a certified incinerator or landfill, respectively; both disposal methods are designed to contain the exposure of residues to the aquatic or terrestrial environment.

Hospitals, pharmacies, clinics, and domestic users—the end users of pharmaceutical chemicals—may have different modes of disposal of unused or expired drug products. Empty or partially empty packages are disposed of according to hospital, pharmacy, or clinic procedures, which typically include collection in appropriate containers and ultimate disposition through certified landfill or incinerator. Expired drug products are generally returned to the manufacturer or distributor, either of whom may dispose of the drug either through landfilling or incineration based on the practice determined for each drug.

At homes, empty or partially empty containers are disposed of through solid waste management systems (*8*) prevailing in the communities, which predominantly include disposal in certified landfills. Domestic waste from pets containing drug residues is similarly disposed of in landfills.

Exposure of pharmaceutical chemicals to the environment and consequent risk to the environment is unlikely to occur through disposal practices by manufacturers or end users. Exposures may occur in the unlikely event of accidental spills during transportation and distribution of raw materials, intermediates, API, or finished product. Such exposures are rarely reported for pharmaceuticals because of controls practiced for packaging and shipment. Environmental exposure pathways for the disposed pharmaceutical chemicals are provided in Figure 5.

Conclusions

Most pharmaceutical active ingredients are produced in smaller quantities than other industrial chemicals.

The FDA cGMPs regulations, which require contained and accountable manufacturing, are designed to assure minimal releases during manufacture.

Regulations on atmospheric emissions and effluent discharges enforced by the U.S. EPA at pharmaceutical manufacturing facilities ensure that the releases are contained within regulatory limits.

Regulations require that the EIC of pharmaceutical residues through human use in the aquatic environment not exceed 1 ppb. If this limit is exceeded, extensive testing and investigations are required to demonstrate that there is no environmental risk at the EEC levels, before the drug applications are approved for human use.

If the predicted environmental concentration of a pharmaceutical chemical in soil is >100 µg/kg (PEC_{soil}) due to use of animal health drugs in nonaquatic food animals, and if the expected introduction concentration from aquaculture facilities ($EIC_{aquatic}$) is >1 µg/L, extensive testing and investigations are required by the FDA to demonstrate that there is no environmental risk before the drug applications are approved for animal use.

Unused, expired, or returned drug products require proper disposition and accountability as per FDA GMPs. Such products are disposed of through incineration or in landfills. The incinerators and landfills for such disposal should be certified and be compliant with applicable emission regulations by the U.S EPA. Also, according to the FDA, end users typically dispose of empty or partially empty containers through domestic solid waste.

In the event pharmaceutical chemical residues are detected in aquatic or terrestrial environmental compartments above the published regulatory limits, a clear relationship between their measured concentration in the environment and the risk to human health or environmental species should be established to arrive at scientifically based risk assessment conclusions.

References and Notes

1. Daughton CG, Ternes TA. Pharmaceuticals and personal care products in the environment: agents of subtle change? Environ Health Perspect 107:907–938 (1999).
2. Halling-Sorensen B, Nors Nielsen S, Lanzky PF, Ingerslev F, Holten Lutzhoft HC, Jergensen SE. Occurrence, fate and effects of pharmaceutical substances in the environment—a review. Chemosphere 36(2):357–393 (1998).
3. Ralloff J. Drugged waters—Does it matter that pharmaceuticals are turning up in water supplies? Sci News 153:187–189 (1998).
4. Velagaleti R. Behavior of pharmaceutical drugs (human and animal health) in the environment. Drug Inform J 31(3):715–722 (1997).
5. Velagaleti R, Winberry MW. Risk assessment of human and animal health drugs in the environment: a chemical fate and environmental effects approach. In: Environmental Toxicology and Risk Assessment: Vol 7 (Little EE, DeLonay AJ, Greenberg BM, eds). ASTM STP 1333. Philadelphia:American Society for Testing and Materials, 1998;356–367.
6. U.S. FDA. Environmental Assessment Technical Assistance Handbook. Washington, DC:U.S. Food and Drug Administration, 1987.
7. U.S. FDA. Retrospective Review of Ecotoxicity Data Submitted in Environmental Assessments for Public Display. Docket no. 96N-0057. Washington, DC:U.S. Food and Drug Administration, 1997.
8. U.S. FDA. Guidance for Industry—Environmental Assessment of Human Drugs and Biologics Applications. CMC 6, Revision 1. Washington, DC:U.S. Food and Drug Administration, 1998.
9. U.S. FDA. Current Good Manufacturing Practice for Active Pharmaceutical Ingredients: Guidance for Industry—Manufacturing, Processing, or Holding Active Pharmaceutical Ingredients. Washington, DC:U.S. Food and Drug Administration, 1998.
10. U.S. FDA. Current Good Manufacturing Practice for Finished Pharmaceuticals. Washington, DC:U.S. Food and Drug Administration, 1995.
11. U.S. Environmental Protection Agency. Pharmaceutical manufacturing category effluent limitations guidelines, pretreatment standards, and new source performance standards; final rule. Fed Reg 63:50388–50437 (1998).
12. Lymann WJ, Reehl WF, Rosenblatt DH. Handbook of Chemical Property Estimation Methods. Washington, DC: American Chemical Society, 1990.
13. Brady NC. The Nature and Properties of Soil. New York: Macmillan Publishing Company, 1974.
14. AHI. Environmental Risk Assessment Working Group. Analysis of Data and Information to Support a PEC_{soil} Trigger Value for Phase I (A Retrospective Review of Ecotoxicity Data from Environmental Assessments Submitted to FDA/CVM to Support the Approval of Veterinary Drug Products in the United States from 1973–1977). Washington DC:Animal Health Institute, 1997.
15. Saepen KRI, Van Leemput LJJ, Wislocki PG, Verschueren C. A uniform procedure to estimate the predicted environmental concentration of the residues of veterinary medicines in soil. Environ Toxicol Chem 16:1977–1982 (1997).
16. EMEA. Guidelines on Environmental Impact Assessments (EIAs) for Veterinary Medicinal Products (VMPs)—Phase I. CVMP/VICH/592/98-FINAL, 20 July 2000 [VICH GL6 (ECOTOXICITY PHASE I), June 2000]. Brussels:European Agency for the Evaluation of Medicinal Products, Committee on Veterinary Medicinal Products, 2000.
17. EMEA. Environmental risk assessment for veterinary medicinal products other than GMO-containing medicinal products. EMEA/CVMP/055/96-FINAL. Brussels: European Agency for the Evaluation of Medicinal Products, Committee on Veterinary Medicinal Products, 1996.